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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,988	05/16/2005	Lasse Leino	OHMAN-002	1914

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EXAMINER	
SHOMER, ISAAC	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
04/07/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,988	LEINO ET AL.	
	Examiner	Art Unit	
	ISAAC SHOMER	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 14 March 2011 has been entered, and the arguments presented therein have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 31-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wille et al. (US Patent 5,843,979).

1) In applicant's arguments dated 14 March 2011 (hereafter referred to as applicant's arguments), applicant contends that Wille fails to raise a prima facie case of

obviousness because there is no motivation to modify the pH of the composition to a range of 6.1 to 7.0, as of applicant's arguments, page 3, last full paragraph. Applicant contends that the argument that the prior art pH range overlaps with the claimed range is "without merit here" because the pH range of 1-12 is so broad as to be almost meaningless, as of applicant's arguments, paragraph bridging pages 3 and 4. Applicant points to two specific examples in Wille that utilize a pH of 5.5, as of Wille, Table III, and 7.2, as of Wille, Table IV, in an attempt to show that Wille does not teach a pH range between 6.1 to 7.0.

None of above arguments are persuasive. The pH range taught by Wille overlaps with the pH range of claim 31. Furthermore, as Wille utilized a pH value of 5.5 for delivery of cis-urocanic acid in one embodiment and a pH value 7.2 for delivery of the same compound in another embodiment, the skilled artisan would have been motivated to have used a pH between those two values to have predictably delivered cis-urocanic acid with a reasonable expectation of success. While the prior art does not disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range establishes a *prima facie* case of obviousness. In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003).

2) In applicant's arguments, applicant contends that Wille's suggested pH range of 1-12 shows that they did not recognize the acid dissociation properties of cis-urocanic acid are important to its immunosuppressive properties, as of applicant's arguments, page 4, second full paragraph. Applicant further points to the Declaration of Dr. Jarmo Laihia to demonstrate the superiority of the claimed pH range.

The examiner disagrees that applicant has shown superior immunosuppressive properties in the claimed pH range. The examiner has responded to the material in the declaration of Dr. Jarmo Laihia below.

Response to Declaration of Dr. Jarmo Laihia and Allegations of Unexpected Results:

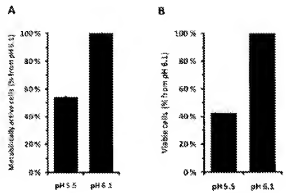
A declaration of Dr. Jarmo Laihia (hereafter referred to as the declaration) was presented with applicant's response dated 14 March 2011. The results of the following experiments were presented, as of page 2, first two paragraph of the declaration:

A: An experiment comparing compositions of pH 5.5 and pH 6.1.

B: An experiment comparing compositions of pH 7.0 and 7.4.

Consistent with the nomenclature, these experiments will be referred to as Experiment A and Experiment B and will be analyzed separately below.

Experiment A: In this experiment, neutrophils were isolated from the peripherial blood of a healthy donor, as of page 2, section A.1 of the delcaration. An equal number of cells were incubated at pH 5.5 (one condition) and pH 6.1 (another condition) for 1 hour, and the average metabolic rate and cell viability rate were measured, as of the declaration, section A2, paragraph bridging pages 2 and 3. This experiment appears to have been done in the absence of cis-urocanic acid (the active substance of the claims). Neutrophils are more metabolically active and more viable at pH 6.1 than pH 5.5, as of page 4, Figure 1 of the declaration (reproduced below):



It is unclear exactly how this result relates to the claimed invention for the following reasons:

I) The experiment in this section is done in the absence of the active substance. In contrast, claim 31 required the presence of an active substance. The claimed pH range is for the pH-of the composition containing the active agent when administered. The art relates to the pH of the composition as well, as of Wille, column 12 lines 60-66. There is no evidence provided that relates to this claimed feature.

ii) There does not appear to be a link between the pH of the composition as administered by the claims to the pH environment of neutrophils, as tested by Experiment A in the declaration. This is because, as neutrophils are blood cells, the skilled artisan would have expected that only modes of administration that are directed to the bloodstream (e.g. intravenous, intra-arterial) would have had an effect on the pH environment of neutrophils.

The instant specification contemplates various modes of administration as of page 8 lines 16-23 of the specification, which include oral administration, intravenous administration, subcutaneous injection, and topical dermal formulations. Of these

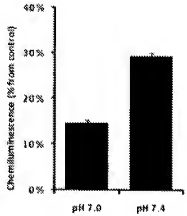
modes of administration, it appears that only intravenous or intradermal administration would have a significant effect on neutrophils (as intravenous injection targets the blood and intradermal injection leads to the lymphatic system and the spleen). The examiner notes that transdermal administration appears to be preferred, as of the above-cited portion of the specification, and there appears to be no link between transdermal administration and the pH environment of neutrophils.

Even if, purely *en arguendo*, the claims were limited to modes of administration that contact directly with blood, for example, intravenous injection, it is unclear that the pH of the administered dosage would have a significant effect on the pH of the whole blood. It is known that blood is buffered at a pH of about 7.3 to 7.4. As such, the presence of a small amount of a composition with a slightly lower or higher pH, such as the claimed dosage, would not likely significantly change the pH of the blood, as the acidity of the dosage would have simply been neutralized by the buffering capacity of the blood.

iii) It is unclear as to how neutrophil cell viability relates to the claimed method for treatment of a local inflammatory disease or disorder. As a neutrophil is a white blood cell which causes immune reactions, the skilled artisan would have expected that a decrease in the metabolic rate and viability of said blood cells would have resulted in a decrease (i.e. inhibition) of immune reaction, as the cells that cause said immune reaction would have been less active. Such a decrease in immune reaction appears to be a desired result, as of instant claim 32.

Experiment B:

In this experiment, declarant compared neutrophils stored at pH 7.0 to neutrophils stores at pH 7.4. The neutrophils were obtained from human blood, as in Experiment A, as of pages 4-5, section B1 of the declaration. In this case, applicant measured a "respiratory burst" activity at the different pH values, as of the declaration, page 5, section B2. In this case, both compositions tested appear to comprise 10 mM cis-urocanic acid, as of page 5, section B3 of the declaration. Declarant's data, as of Figure 2 (reproduced below), shows that there is a greater measured signal in the composition with a pH of 7.4 than pH 7.0.



Increased chemiluminescence is understood to be indicative of increased speed of the respiratory burst reaction, as of page 5, section B2 of the declaration. As such, the above-reproduced results show that there is increased inhibition of respiratory burst of neutrophils at pH 7.0 as compared with pH 7.4.

Nevertheless, there does not appear to be a link between the pH of the composition as administered by the claims to the pH environment of neutrophils, as tested by declarant. This is because, as neutrophils are blood cells, the skilled artisan

would have expected that only modes of administration that are directed to the bloodstream (e.g. intravenous, intra-arterial) would have had an effect on the pH environment of neutrophils.

The instant specification contemplates various modes of administration as of page 8 lines 16-23 of the specification, which include oral administration, intravenous administration, subcutaneous injection, and topical dermal formulations. Of these modes of administration, it appears that only intravenous or intradermal administration would have a significant effect on neutrophils (as intravenous injection targets the blood and intradermal injection leads to the lymphatic system and the spleen). The examiner notes that transdermal administration appears to be preferred, as of the above-cited portion of the specification, and there appears to be no link between transdermal administration and the pH environment of neutrophils.

Even if, purely *en arguendo*, the claims were limited to modes of administration that contact directly with blood, for example, intravenous injection, it is unclear that the pH of the administered dosage would have a significant effect on the pH of the whole blood. It is known that blood is buffered at a pH of about 7.3 to 7.4. As such, the presence of a small amount of a composition with a slightly lower or higher pH, such as the claimed dosage, would not likely significantly change the pH of the blood, as the acidity of the dosage would have simply been neutralized by the buffering capacity of the blood.

For these reasons, the declaration submitted on 14 March 2011 by Dr. Jarmo Laihia is not probative of non-obviousness.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612